

Application No. 10/506,748
 Amendment Dated 03/14/2006
 Reply to Office Action of 12/14/2005

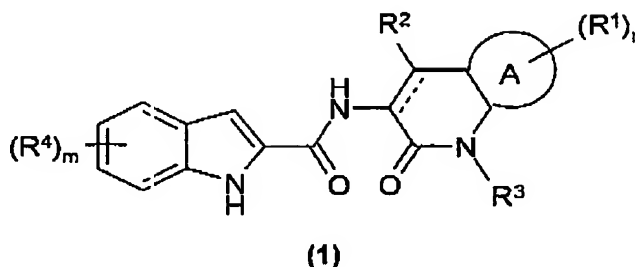
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-15. (Cancelled)

16. (New) A compound of formula (1):



wherein

----- is a single or double bond;

A is phenylene or heteroarylene;

m is 1;

n is 0, 1, or 2;

R¹ is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl, *N*-C₁₋₄alkylcarbamoyl, *N,N*-(C₁₋₄alkyl)₂carbamoyl, sulphamoyl, *N*-C₁₋₄alkylsulphamoyl, *N,N*-(C₁₋₄alkyl)₂sulphamoyl, -S(O)_bC₁₋₄alkyl (wherein b is 0, 1, or 2), C₁₋₄alkyl, C₂₋₄alkenyl, C₂₋₄alkynyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkanoyloxy, hydroxyc₁₋₄alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, and trifluoromethoxy; or

when n is 2, the two R¹ groups, together with the carbon atoms of A to which they are attached, may form a 4- to 7-membered ring, optionally containing 1 or 2 heteroatoms independently selected from O, S, and N, and optionally being substituted with one or two methyl groups;

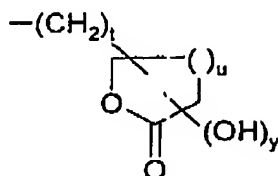
R⁴ is chloro;

R² is hydrogen, hydroxy, or carboxy;

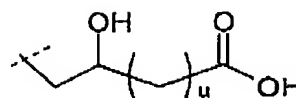
R³ is selected from hydrogen, hydroxy, C₁₋₄alkoxy, C₁₋₄alkanoyl, carbamoyl, C₃₋₇cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C₁₋₄)alkyl, aryl, heterocyclyl, C₁₋₄alkyl (optionally substituted with 1 or 2 R^a groups), and groups of the formulae B and B'

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(B)



(B')

wherein y is 0 or 1, t is 0, 1, 2, or 3; and u is 1 or 2;

provided that the hydroxy group is not a substituent on the ring carbon adjacent to the ring oxygen;

R⁸ is independently selected from hydroxy, C₁₋₄alkoxyC₁₋₄alkoxy, hydroxyC₁₋₄alkoxy, 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, aryl, heterocyclyl, C₃₋₇cycloalkyl, C₁₋₄alkanoyl, C₁₋₄alkoxy, C₁₋₄alkylS(O)_b- (wherein b is 0, 1, or 2), C₃₋₆cycloalkylS(O)_b- (wherein b is 0, 1, or 2), arylS(O)_b- (wherein b is 0, 1, or 2), heterocyclylS(O)_b- (wherein b is 0, 1, or 2), benzylS(O)_b- (wherein b is 0, 1, or 2), -N(OH)CHO, -C(=N-OH)NH₂, -C(=N-OH)NHC₁₋₄alkyl, -C(=N-OH)N(C₁₋₄alkyl)₂, -C(=N-OH)NHC₃₋₆cycloalkyl, -C(=N-OH)N(C₃₋₆cycloalkyl)₂, -COCOOR⁹, -C(O)N(R⁹)(R¹⁰), -NHC(O)R⁹, -C(O)NH₂SO₂(C₁₋₄alkyl), -NH₂SO₂R⁹, (R⁹)(R¹⁰)NSO₂-, -COC₂H₄OR¹¹, (R⁹)(R¹⁰)N-, and -COOR⁹;

R⁹ and R¹⁰ are independently selected from hydrogen, hydroxy, C₁₋₄alkyl (optionally substituted with 1 or 2 R¹³), C₃₋₇cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C₁₋₄alkyl), trihalo(C₁₋₄alkyl), aryl, heterocyclyl, and heterocyclyl(C₁₋₄alkyl); or

R⁹ and R¹⁰ together with the nitrogen to which they are attached form a 4- to 6-membered ring where the ring is optionally substituted on carbon with 1 or 2 substituents independently selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl, C₁₋₄alkoxy, and heterocyclyl, or the ring may be optionally substituted on two adjacent carbons with -O-CH₂-O- to form a cyclic acetal wherein one or both of the hydrogens of the -O-CH₂-O- group may be replaced by a methyl;

R¹³ is selected from hydroxy, halo, trihalomethyl, and C₁₋₄alkoxy; and

R¹¹ is independently selected from hydrogen, C₁₋₄alkyl, and hydroxyC₁₋₄alkyl;

or a pharmaceutically acceptable salt or prodrug thereof.

17. (New) A compound of claim 16i, wherein

R³ is selected from hydrogen, hydroxy, C₁₋₄alkoxy, C₁₋₄alkanoyl, carbamoyl, C₃₋₇cycloalkyl (optionally substituted with 1 or 2 hydroxy groups, cyano(C₁₋₄alkyl), phenyl, morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazol danyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino,

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pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopyridinyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl, tetrahydrothiopyranyl, 1-oxotetrahydrothiopyranyl, 1,1-dioxotetrahydrothiopyranyl, and C₁₋₄alkyl (optionally substituted with 1 or 2 R⁹ groups); R⁹ and R¹⁰ are independently selected from hydrogen, hydroxy, C₁₋₄alkyl (optionally substituted with 1 or 2 R¹³ groups), C₃₋₇cycloalkyl (optionally substituted with 1 or 2 hydroxy groups), cyano(C₁₋₄)alkyl, trihalo C₁₋₄alkyl, aryl, heterocyclyl, and heterocyclyl(C₁₋₄alkyl); or R⁹ and R¹⁰ together with the nitrogen to which they are attached form a 4- to 6-membered ring where the ring is optionally substituted on carbon with 1 or 2 substituents selected from oxo, hydroxy, carboxy, halo, nitro, cyano, carbonyl, and C₁₋₄alkoxy, or the ring may be optionally substituted on two adjacent carbons with -O-CH₂-O- to form a cyclic acetal wherein one or both of the hydrogens of the -O-CH₂-O- group may be replaced by a methyl;

R⁸ is independently selected from hydroxy, C₁₋₄alkoxy, C₁₋₄alkoxy, hydroxyC₁₋₄alkoxy, 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, aryl, heterocyclyl, C₃₋₇cycloalkyl, C₁₋₄alkanoyl, C₁₋₄alkoxy, C₁₋₄alkylS(O)_b- (wherein b is 0, 1, or 2), C₃₋₆cycloalkylS(O)_b- (wherein b is 0, 1, or 2), arylS(O)_b- (wherein b is 0, 1, or 2), heterocyclylS(O)_b- (wherein b is 0, 1, or 2), benzylS(O)_b- (wherein b is 0, 1, or 2), -N(OH)CHO, -C(=N-OH)NH₂, -C(=N-OH)NHC₁₋₄alkyl, -C(=N-OH)N(C₁₋₄alkyl)₂, -C(=N-OH)NHC₃₋₆cycloalkyl, -C(=N-OH)N(C₃₋₆cycloalkyl)₂, -COOOR⁹, -C(O)N(R⁹)(R¹⁰), -NHC(O)R⁹, -C(O)NHSO₂(C₁₋₄alkyl), -NHSO₂R⁹, (R⁹)(R¹⁰)NSO₂-, -COCH₂OR¹¹, (R⁹)(R¹⁰)N-, and -COOR⁹;

R¹³ is selected from hydroxy, halo, trifluoromethyl, and C₁₋₄alkoxy; and

R¹¹ is selected from hydrogen, C₁₋₄alkyl, and hydroxyC₁₋₄alkyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

18. (New) A compound of claim 16, wherein:

R³ is selected from cyanoC₁₋₄alkyl and C₁₋₄alkyl (optionally substituted with 1 or 2 R⁸ groups);

R⁸ is independently selected from hydroxy, phenyl, 2,2-dimethyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxan-4-yl, 2,2-dimethyl-1,3-dioxan-5-yl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, triazolyl, tetrazolyl, imidazolyl, pyrrolidinyl, piperidyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkylS(O)_b- (wherein b is 0, 1, or 2), -C(O)N(R⁹)(R¹⁰), -COOR⁹, -C(O)NHSO₂Me, -C(=N-OH)NH₂, -C(=N-OH)NHC₁₋₄alkyl, -C(=N-OH)N(C₁₋₄alkyl)₂, and -NHSO₂R⁹; and

R⁹ and R¹⁰ are independently selected from hydrogen, hydroxy, and C₁₋₄alkyl optionally substituted with R¹³ (wherein R¹³ is C₁₋₄alkoxy or hydroxy); or

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R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 6-membered ring where the ring may be optionally substituted on carbon with 1 or 2 hydroxy groups or carboxy groups), or the ring may be optionally substituted on two adjacent carbons with $-O-CH_2-O-$ to form a cyclic acetal wherein one or both of the hydrogens of the $-O-CH_2-O-$ group may be replaced by a methyl;
or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

19. (New) A compound of claim 16, wherein:

R^8 is selected from cyano, C_{1-4} alkyl, and C_{1-4} alkyl (optionally substituted with 1 or 2 R^8 groups);

R^8 is independently selected from hydroxy, 2,2-dimethyl-1,3-dioxolan-4-yl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, tetrazolyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkylS(O)_b (wherein b is 0, 1, or 2), $-C(O)N(R^9)(R^{10})$, $-COOR^9$, $-C(O)NHSO_2Me$, and $-C(=N-OH)NH_2$; and

R^9 and R^{10} are independently selected from hydrogen, hydroxy, and C_{1-4} alkyl optionally substituted with R^{13} (wherein R^{13} is C_{1-4} alkoxy or hydroxy); or

R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 6-membered ring selected from piperidine, 4-hydroxypiperidine, pyrrolidine, 3,4-dihydroxypyrrolidine, and the dimethylacetal of 3,4-dihydroxypyrrolidine;
or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

20. (New) A compound of claim 16, wherein:

A is phenylene;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

21. (New) A compound of claim 16, wherein:

A is heteroarylene;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

22. (New) A compound of claim 16, wherein:

--- is a single bond;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

23. (New) A compound of claim 16 selected from:

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5-chloro-*N*-[1-(methoxycarbonylmethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-1*H*-indole-2-carboxamide;
N-[1-(carboxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-5-chloroindole-2-carboxamide;
5-chloro-*N*-(2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-[2-oxo-1-[2-oxo-2-(pyridin-2-ylamino)ethyl]-1,2,3,4-tetrahydroquinolin-3-yl]-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-[2-(methylthio)ethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-[2-(methylsulphiny)ethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-[2-(methylsulphonyl)ethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(2-oxo-1-[2-oxo-2-(1,3,4-thiadiazol-2-ylamino)ethyl]-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-[2-[(6-methylpyridin-2-yl)amino]-2-oxoethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(2-oxo-1-[2-oxo-2-(pyridin-3-ylamino)ethyl]-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-[2-[(5-methyl-1,3,4-thiadiazol-2-yl)amino]-2-oxoethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-[2-[(5-ethyl-1,3,4-thiadiazol-2-yl)amino]-2-oxoethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-[2-[(4-cyano-1*H*-pyrazol-3-yl)amino]-2-oxoethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-[2-[(4-methyl-1,3-thiazol-2-yl)amino]-2-oxoethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-[2-[(6-chloropyridin-3-yl)amino]-2-oxoethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-[2-[(3-hydroxypyridin-2-yl)amino]-2-oxoethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(2-oxo-1-[2-oxo-2-[(pyridin-2-ylmethyl)amino]ethyl]-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(2-oxo-1-[2-oxo-2-(pyridin-4-ylamino)ethyl]-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;

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5-chloro-*N*-(1-{2-[(1-methyl-1*H*-pyrazol-5-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(1,3-dimethyl-1*H*-pyrazol-5-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(2-oxo-1-{2-oxo-2-[(pyrazin-2-ylmethyl)amino]ethyl}-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(6-fluoropyridin-3-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(2-hydroxypyrimidin-4-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(2-oxo-1-{2-oxo-2-(pyrimidin-4-ylamino)ethyl}-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(1-ethyl-1*H*-pyrazol-5-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(2-oxo-1-{2-oxo-2-[(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)amino]ethyl}-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(4-hydroxypyrimidin-2-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(3-methylpyridin-2-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(6-chloropyridazin-3-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(1*H*-imidazol-2-yl)methyl]amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(1-methyl-1*H*-pyrazol-3-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(2-oxo-1-{2-oxo-2-(2*H*-tetrazol-5-ylamino)ethyl}-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(3-ethyl-1*H*-pyrazol-5-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(5-fluoropyridin-2-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
N-(1-{2-[(6-bromopyridin-3-yl)amino]-2-oxoethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-5-chloro-1*H*-indole-2-carboxamide;

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5-chloro-*N*-[1-(2-hydroxyethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-1*H*-indole-2-carboxamide;
5-chloro-*N*-{1-[(2,2-dimethyl-1,3-dioxan-5-yl)methyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;
5-chloro-*N*-{1-[3-hydroxy-2-(hydroxymethyl)propyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;
5-chloro-*N*-{1-(2,3-dihydroxypropyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;
5-chloro-*N*-{1-(3-hydroxy-2-oxopropyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;
5-chloro-*N*-{1-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;
5-chloro-*N*-(1-{2-[(methylsulfonyl)amino]ethyl}-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
N-{1-[2-(acetylamino)ethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-5-chloro-1*H*-indole-2-carboxamide;
5-chloro-*N*-(2-oxo-1-{2-[(trifluoroacetyl)amino]ethyl}-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide;
5-chloro-*N*-{1-(3-hydroxypropyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-1*H*-indole-2-carboxamide;
N-{1-[(2*Z*)-2-amino-2-(hydroxyimino)ethyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-5-chloro-1*H*-indole-2-carboxamide;
5-chloro-*N*-(6-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-1*H*-indole-2-carboxamide; and
5-chloro-*N*-[6-(methyloxy)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl]-1*H*-indole-2-carboxamide;
or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof.

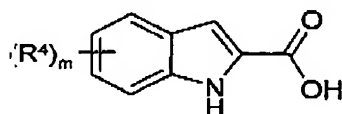
24. (New) A pharmaceutical composition which comprises a compound of claim 16, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, in association with a pharmaceutically acceptable diluent or carrier.

25. (New) A method for the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia, or obesity in a warm-blooded animal, comprising administering a compound of claim 16, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

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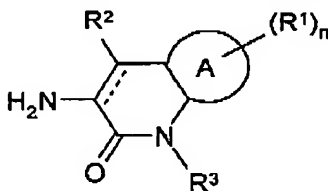
26. (New) A method for the treatment of type 2 diabetes in a warm-blooded animal, comprising administering a compound of claim 16, or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

27. (New) A process for the preparation of a compound claim 16, which process comprises:
reacting an acid of the formula (2)



(2)

or an activated derivative thereof; with an amine of formula (3)



(3)

and thereafter if necessary

- i) converting a compound of the formula (1) into another compound of the formula (1);
- ii) removing any protecting groups; or
- iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.